A multicentric, placebo-controlled, double-blind clinical trial of β-sitosterol (phytosterol) for the treatment of benign prostatic hyperplasia

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Objective To report the results of a double-blind, placebo-controlled trial to evaluate Azuprostat®, a β-sitosterol, in patients with symptoms of outlet obstruction caused by benign prostatic hyperplasia (BPH).

Patients and methods A randomized, double-blind and placebo-controlled clinical trial was conducted to assess the efficacy and safety of 130 mg free β-sitosterol (phytosterol) daily, using the international prostate symptom score (IPSS) as the primary outcome variable. In total, 177 patients with BPH were recruited for 6 months of treatment in 13 study centres. In addition to the relative difference in the IPSS, changes in quality of life, peak urinary flow rate (Q_{max}) and post-void residual urinary volume (PVR) were recorded. The drug used in the trial consisted of a chemically defined extract of phytosterols, derived for example from species of *Pinus*, *Picea* or *Hypoxis*, with β-sitosterol as the main component.

Results There were significant ($P < 0.01$) improvements over placebo in those treated with β-sitosterol; the mean difference in the IPSS between placebo and β-sitosterol, adjusted for the initial values, was 5.4 and in the quality-of-life index was 0.9. There were also significant improvements in the secondary outcome variables, with an increase in Q_{max} (4.5 mL/s) and decrease in PVR (33.5 mL) in favour of β-sitosterol when adjusted for the changes after placebo.

Conclusion These results show that β-sitosterol is an effective option in the treatment of BPH.

Keywords β-sitosterol therapy, symptom score, benign prostatic hyperplasia

Introduction

Therapies with confirmed efficacy in treating BOO caused by BPH should be minimally invasive, economical and of low risk [1–4]; TURP is the 'gold standard' against which these alternative treatments must be compared for efficacy and safety [5]. An interest in medicinal alternatives to surgical intervention led to the development of 5-α-reductase inhibitors [6–8] and alpha adrenergic blockers [9–12] that are now established treatments for symptomatic BPH in many countries.

There has been a long tradition in some European countries for the use of drugs of plant origin in the treatment of BPH. A mixture of constituents from plant products, some of which may be active and others not, has drawn criticism of these agents and their mode of action. Few have been evaluated in controlled clinical trials, but this deficiency is now being addressed [1,13,17].

This study was designed in accordance with the recommendations of the International Consultation on BPH (1991 and 1993) [13,14] and reports the results of a double-blind, placebo-controlled trial to evaluate Azuprostat®, a β-sitosterol, in patients with symptoms of BOO caused by BPH. The drug used in this trial consists of a chemically defined extract of phytosterols, derived for example from species of *Pinus*, *Picea* or *Hypoxis*, with β-sitosterol as the main component.

Patients and methods

Patients

The study was conducted between October 1993 and September 1994 at 13 private urological centres in Germany, with a total recruitment of 177 patients; 89 patients were allocated randomly to receive placebo and 88 to β-sitosterol. A 4-week wash-out period was required for all patients currently on symptomatic medication for benign prostatic disorders. Concomitant medication with drugs acting on the hormonal axis of the prostate, cimetidine, anticholinergics, sympathomimetics and psychotropic drugs were discontinued in patients 2 weeks before entering the trial. The conduct of the study was supervised

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Table 1 Patients characteristics at recruitment

Characteristic	Placebo	β-Sitosterol	P (t-test)
Mean (SD)			
Age (years)	65.9 (7.43)	64.8 (8.06)	0.355
Height (cm)	174.6 (6.11)	173.9 (5.36)	0.484
Body weight (kg)	78.7 (7.91)	77.4 (8.05)	0.274
Pre-treatment drug therapy (%)	35.9	45.9	0.112*
Concomitant allowed therapies (%)	23.5	27.5	0.624*
IPSS (points)	14.9 (5.17)	16.0 (4.58)	0.144
Quality of life (points)	3.0 (0.91)	3.2 (0.79)	0.158
Peak flow (mL/s)	11.3 (2.70)	10.6 (3.33)	0.116
Mean voided volume (mL)	246.8 (98.8)	236.5 (94.5)	0.477
Residual urine volume (mL)	63.1 (26.36)	63.4 (28.97)	0.935

*Chi-square test.

by extensive monitoring; in addition, the responsible specialists in each centre nominated a second person (study assistant) to supervise the patients' appointments and internal quality control. Table 1 lists the patients' characteristics of both groups at the beginning of the study.

Methods

After taking the patients' history at the initial visit, the symptom score and quality-of-life (QOL) index were recorded using the IPSS questionnaire. The post-void residual urinary volume (PVR) was measured by transabdominal ultrasonography after measuring urinary flow rate and voiding volume. The prostatic volume was not assessed by ultrasonography. Patients underwent a DRE and blood was sampled for laboratory tests including liver and renal function, PSA level and a blood cell count; a urine sample was also cultured. Inclusion and exclusion criteria are shown in Table 2.

During the follow-up, each patient was evaluated monthly (seven visits in total) and on each visit compliance was recorded by counting the capsules not used in the previous month. Side-effects and possible concomitant medication were recorded and evaluated according to the exclusion criteria. The IPSS and QOL index were assessed, the PVR and urinary flow rate measured, and the medication for the following month supplied. Laboratory tests, conducted at the initial visit, were repeated after 6 months. A subjective assessment of efficacy was obtained by questionnaire at the final follow-up visit.

Medication

The term β-sitosterol represents a chemically defined extract of phytosterols with β-sitosterol as the main

Table 2 Inclusion and exclusion criteria

Inclusion criteria
IPSS of at $\geqslant 6$ points
Residual urinary volume 30–150 mL
$Q_{max} \leqslant 15$ mL/s, at a voiding volume of $\geqslant 150$ mL
Benign enlargement of the prostate (DRE)
Age 50–80 years
Body weight 55–100 kg

Exclusion criteria
IPSS of < 6 points
Prostatic malignancy
PSA level > 10 ng/mL
Bacterial prostatitis
Urinary infection
History of acute urinary retention
History of surgical prostatic intervention
Need for surgical intervention in case of urethral stricture or bladder diverticulae
Bladder stones
Phimosis and meatal stenosis
Insulin-dependent diabetes
Abnormal laboratory values, e.g. glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, alkaline phosphatase, creatinine
Severe cardiopulmonary disease
Neurological or psychological disorders
Concomitant prostatotropic treatment
Abuse of alcohol or drugs
Expected non-compliance

component. In contrast to the glycosidic phytosterols originally in plant sources, the drugs used in current therapy are defined compositions of free phytosterolic components (aglycons) produced by current manufacturing processes (Pharmaceutical Monograph for the European Pharmacopoeia, in preparation). Each patients took two capsules per day, each containing 65 mg either of β-sitosterol (Azuprostat®, Azupharma, Germany) or placebo over a period of 6 months.

Each centre had been supplied with one package of medication for each patient, numbered according to a randomized sequence, with each of these containing smaller boxes with the medication calculated for one month of therapy. All capsules were manufactured to meet the requirements of the study; there were no differences in size, shape, colour, weight, smell or taste between active or placebo capsules and all were packaged in the same blister-packs.

Statistical analysis

The primary endpoint of the study was the relative difference in the IPSS between the groups, measured by the percentage change from the initial to the final follow-up visit. The QOL index, PVR and peak urinary flow rate

(Q_{max}) were assessed as secondary outcome variables. To detect a difference of 3 points (SD of 5 points) in the mean IPSS during the 6 months of treatment between the groups (considered as clinically relevant), 61 patients were needed in each treatment group to give a power of 95% ($\alpha = \beta = 0.05$). With an expected withdrawal rate of about 15 patients per treatment arm and the reduced efficiency of the non-parametric method, the planned size of the treatment groups was increased to 90 patients. The IPSS scores were analysed statistically using the one-sided Mann–Whitney test at the 5% level of significance. All other tests of significance were considered descriptive. The intention-to-treat analysis was used to evaluate the results for the IPSS; for patients who did not complete the 6 months of treatment, the last value obtained was carried forward to 6 months.

Results

All but three centres recruited a median of 18 (range 11–24) patients. There were no violations of the exclusion criteria, but some inclusion criteria were not met. One patient (on β-sitosterol) was 49 years old at the beginning of the study and five others exceeded the age limit (two on placebo, three on β-sitosterol). Two patients had a PVR of < 30 mL (one on placebo, 10 mL, and one on β-sitosterol, 20 mL) and one patient had a PVR of 194 mL.

Withdrawals and side-effects

Twenty-two patients did not complete the 6 month period of treatment, 11 in each group. In the placebo group, one patient was excluded after an acute myocardial infarction. In the β-sitosterol group, one patient was

Table 3 Primary and secondary outcomes after 6 months of therapy with β-sitosterol or placebo (mean [SD])

	Initial	6 months	Difference
β-sitosterol			
IPSS (points)	16.0 (4.58)	7.8 (4.93)	−8.2 (5.74)
Quality of life (points)	3.3 (0.79)	1.4 (0.65)	−1.8 (1.02)
Q_{max} (mL/s)	10.6 (3.33)	19.4 (8.62)	8.9 (8.86)
PVR (mL)	63.4 (29.0)	25.6 (28.8)	−37.5 (37.2)
Placebo			
IPSS (points)	14.9 (5.17)	12.1 (5.56)	−2.8 (4.18)
Quality of life (points)	3.1 (0.91)	2.2 (0.98)	−0.9 (0.91)
Q_{max} (mL/s)	11.3 (2.7)	15.7 (6.12)	4.4 (5.87)
PVR (mL)	63.1 (26.36)	59.1 (44.12)	−4.1 (33.57)

withdrawn because of recurrent indigestion under medication. Two patients had sudden cardiac infarction, one suffered a stroke with hemiparesis and one patient decided to withdraw because he felt a rapid worsening of symptoms. All other withdrawals were for non-compliance caused by the patient's decision, or by being unable to attend regular follow-up checks in the centres; this is a general problem in out-patient trials with older participants, rather than a consequence of the treatment. None of the severe incidents in the β-sitosterol group was attributable to the drug and decoding of the randomization was unnecessary.

Outcome

Most (87.5%) of the patients completed the study in accordance with the protocol to the 6-month follow-up; the earlier withdrawals were incorporated into the
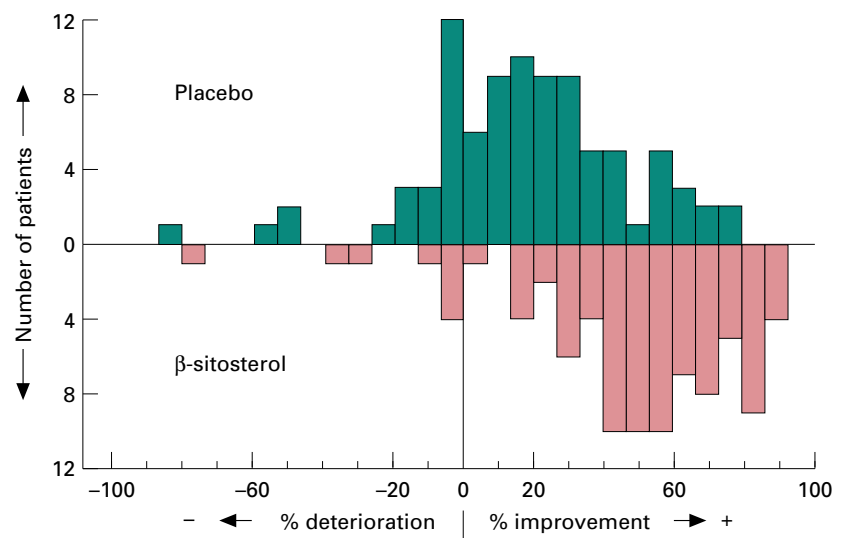

Fig. 1. Individual relative changes (%) in the IPSS from the initial to final visit. Green, Placebo. Red, β-sitosterol.

intention-to-treat analysis. Both the IPSS and the secondary variables showed significant ($P<0.01$) improvements in the β-sitosterol group, but improvements to unexpected levels also occurred in the placebo group (Table 3). The improvement in the IPSS with β-sitosterol and placebo was 51% and 19%, respectively.

To assess the improvement with β-sitosterol over placebo, adjusting for the initial values in IPSS, the difference in the changes in the IPSS (and other variables) for the groups was also calculated; the mean advantage of β-sitosterol was then 5.4 IPSS points and the corresponding advantage in QOL index was 0.9 points, for Q_{max} 4.5 mL/s and PVR 33.5 mL in favour of β-sitosterol (Table 3).

Nearly half of the total improvement had occurred in the first month in both groups; the improvement increased more slowly to 6 months in both groups, but with less variation in the profile of the β-sitosterol group. The advantage with β-sitosterol increased from 2.6 at 1 month to 4.5 and 5.4 at 3 and 6 months, respectively. The better performance of β-sitosterol is illustrated in Fig. 1; two histograms, one above and one below the baseline, show the frequency (number of patients) with similar individual relative percentage changes from the initial to the final visit in both treatment groups.

Discussion

Plant-derived drugs, although well established in the treatment of BPH, are rarely considered in international scientific discussion on the treatment strategies for BPH. In 1991, the International Consensus Committee on BPH stated that 'Although these extracts have been widely used for many years in various countries, they have not yet been studied adequately to determine their exact effectiveness and their mode of action.' [13]. Since then, pharmacological and clinical research on phytotherapeutic compounds for BPH has increased with the growing interest of health professionals and patients in such low-risk, low-cost drugs [1,16]. Berges *et al.* reported the use of β-sitosterol (phytosterols) in patients with BPH [17]; in this randomized, placebo-controlled, double-blind trial, the efficacy, safety, benefits and risks of β-sitosterol therapy were clearly established.

The present multicentre trial used the IPSS as the primary outcome variable, according to international recommendations [13,14] and showed a significant advantage of β-sitosterol over placebo and a favourable benefit-risk ratio. There was a significant reduction in the IPSS in patients receiving β-sitosterol compared with those receiving placebo and an improvement in the subjective evaluation of quality of life; Q_{max} and PVR were also significantly improved compared with placebo. No relevant side-effects were observed in the treatment group.

The results from the present trial are comparable with those in an earlier pilot study with β-sitosterol [15] and with the outcome reported by Berges *et al.* [17]. The design of the latter and the present trial were similar [13,14], but differed in the symptom score used and in the dosage regimen. Berges *et al.* used a modified Boyarsky score [18] as the primary and the IPSS as a secondary variable, recorded only three times during the follow-up; the dose regimen was 20 mg three times daily, whereas 65 mg was administered twice daily in the present study. The limited availability of dose-response relationships for such phytotherapeutic drugs remains a point of criticism. In the present study, the higher dose used has been confirmed in practice by almost 15 years of empirical experience and is fully within the registered dose range for the BPH indication in Germany.

In both trials, treatment with β-sitosterol produced a greater improvement than did placebo for the symptom score, Q_{max} and QOL index. The PVRs were comparable at recruitment but were reduced significantly in both trials (by 33 mL more than placebo in the present study and by 24 mL in [17]).

The improvement in the assessed variables was more rapid in the first month of therapy than later (with β-sitosterol and placebo). Such improvement profiles are similar to those reported in other studies of BPH treatment using alpha-blocking agents or finasteride [8,12,19]. The present trial showed slightly more rapid changes initially than did that by Berges *et al.* [17], with a difference of 2.6 points over placebo after 4 weeks.

However, the statistically defined endpoint in the present trial was not the absolute IPSS profile but the relative difference in the IPSS between the placebo and β-sitosterol groups measured as the percentage change from the initial to the final visit (Fig. 1). This analysis highlights the individual changes in IPSS and shows the 'benefit' to patients in both groups.

In contrast with the present study, randomized trials with finasteride have used the change in prostatic volume as the endpoint [6,8,21]. Considering the mechanism of action of finasteride, this is the primary and most important outcome variable in studies with this drug. In the present trial, it was not deemed necessary to assess this variable because no reduction could be expected with β-sitosterol [24]. This was also confirmed by the results of Berges *et al.* [17] where improvements occurred with no change in prostatic volume. For finasteride, the reported change from baseline in Q_{max} was up to 4 mL/s after 10–12 months [20] and the improvement in symptom score was 3.6 after 36 months of long-term follow-up [8] or 6.4 (4 in placebo) as reported by others [22,23]. These outcomes, calculated from baseline, are similar to the improvements over placebo observed in the present study.

Trials with alpha-receptor blocking agents show a range of mostly significant improvements, lower or higher than those in the present study. With alfuzosin, Jardin *et al.* [10] reported an improvement of 4 points in the symptom score, 3.1 mL/s in Q_{max} and 31 mL (39%) in PVR. The results reported for doxazosin were an improvement of 39% for the total score [19] and 82% and 90% for the irritative and obstructive symptoms, respectively [11], while the changes in Q_{max} were up to 2.9 mL/s [19] or 45% [11]. PVRs were monitored in two of the studies [9,11] and showed reductions of 15–72%. Similar results were observed with prazosin [11], while the results for terazosin [12,25] showed improvements in the symptom score of up to 5.0 and up to 5.4 mL/s for Q_{max}. Other reported changes from baseline in Q_{max} showed improvements of 10, 6.9 and 6.2 mL/s for indoramin, prazosin and phenoxybenzamine, respectively [26–28]. However, all these results should be compared with the corresponding changes in the associated placebo groups to calculate the actual improvement over placebo.

It is well known that placebo effects occur in pharmacological therapies in general and particularly in patients with BPH who wish to avoid operative intervention [29]; responses of up to 40% or more have been reported [30–32]. The placebo response in the present study was about 19% in the IPSS, 29% in the QOL index and 43% in Q_{max}, with no effect on PVR. This placebo effect is comparable with that obtained in the pilot study with the same drug [15] and to the results for other drugs used to treat BPH. The corresponding placebo response reported by Berges *et al.* [17] was lower with their chosen symptom score, but was more apparent in the PVR. Thus, the placebo response can be accounted for by normal statistical variability and appears to be a usual response for patients with BPH as characterized in this study. Further research should now focus on the possible biochemical mechanisms of β-sitosterol action in patients with BPH.

Acknowledgement

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